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In Vivo Validation of a Catheter-Based Near-Infrared Spectroscopy System for Detection of Lipid Core Coronary Plaques

Initial Results of the SPECTACL Study

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OBJECTIVES To determine whether catheter-based near-infrared spectroscopy (NIRS) signals obtained with a novel catheter-based system from coronaries of patients are similar to those from autopsy specimens and to assess initial safety of NIRS device.

BACKGROUND An intravascular NIRS system for detection of lipid core-containing plaques (LCP) has been validated in human coronary autopsy specimens. The SPECTACL (SPECTroscopic Assessment of Coronary Lipid) trial was a parallel first-in-human multicenter study designed to demonstrate the applicability of the LCP detection algorithm in living patients.

METHODS Intracoronary NIRS was performed in patients undergoing percutaneous coronary intervention. Acquired spectra were blindly compared with autopsy NIRS signals with multivariate statistics. To meet the end point of spectral similarity, at least two-thirds of the scans were required to have >80% of spectra similar to the autopsy spectra.

RESULTS A total of 106 patients were enrolled; there were no serious adverse events attributed to NIRS. Spectroscopic data could not be obtained in 17 (16%) patients due to technical limitations, leaving 89 patients for analysis. Spectra from 30 patients were unblinded to test the calibration of the LCP detection algorithm. Of the remaining 59 blinded cases, after excluding 11 due to inadequate data, spectral similarity was demonstrated in 40 of 48 spectrally adequate scans (83% success rate, 95% confidence interval: 70% to 93%, median spectral similarity/pullback: 96%, interquartile range 10%). The LCP was detected in 58% of 60 spectrally similar scans from both cohorts.

CONCLUSIONS This intravascular NIRS system safely obtained spectral data in patients that were similar to those from autopsy specimens. These results demonstrate the feasibility of invasive detection of coronary LCP with this novel system. (SPECTACL: SPECTroscopic Assessment of Coronary Lipid; NCT00330928) (J Am Coll Cardiol Img 2009;2:858–68) © 2009 by the American College of Cardiology Foundation

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Lipid core-containing coronary plaques (LCP), which are implicated in the progression of coronary atherosclerosis and are thought to be the cause of most acute coronary syndromes (ACS), cannot be detected by conventional diagnostic methods (1,2). A diagnostic modality that could detect LCP could be used for improved risk stratification and as a guide to therapy to prevent future cardiovascular events (3).

Near-infrared spectroscopy (NIRS), which is routinely used in science and industry to determine the chemical composition of substances, has the potential to identify LCP in patients (4). Studies conducted by several groups over the last decade have consistently documented the ability of NIRS to identify lipid core atherosclerotic plaques in autopsy specimens (5–9). A catheter-based NIRS system suitable for detection of intracoronary LCP in patients has recently been developed, and its ability to identify LCP has been validated in a human coronary autopsy study (10).

The SPECTACL (SPECTroscopic Assessment of Coronary Lipid) study was conducted to determine whether NIRS signals obtained in the coronary arteries of living patients are spectrally similar to those obtained in the autopsy validation study (Fig. 1) (11). Secondary goals of the study were to obtain evidence supporting the expected safety of this catheter-based NIRS system and to identify the prevalence of LCP, as detected by NIRS, in coronary arterial segments in living patients.

METHODS

NIRS system. The NIRS system consists of a 3.2-F rapid exchange catheter, a pullback and rotation (PBR) device, and a console (Fig. 2). The study was initiated with a "primed" catheter, which required a saline flush to prime the imaging window and a complex connection to a prototype PBR device. In the latter portion of the study, a redesigned "sealed" catheter was used, which obviated the need for priming and simplified the connection to the PBR device.

The system acquires approximately 1,000 NIRS measurements/12.5 mm of artery scanned. Each measurement interrogates an area of 1 to 2 mm2 of lumen surface perpendicular to the long axis of the catheter and centered on the catheter's optical tip. The majority of the NIRS tissue information is obtained from a depth of 1 mm or less in the direction from the luminal surface toward the adventitia.

The measurement of the probability of LCP for each scanned arterial segment is displayed as a map, with the x-axis indicating the pullback position in millimeters and the y-axis the circumferential position of the measurement in degrees. The algorithm displays the probability of LCP at the interrogation site by using a false color scale from red (low probability) to yellow (high probability). The entire display is termed a chemogram (Fig. 3).

To enhance interpretation of the chemogram, a summary metric (the block chemogram) is computed to display the probability that an LCP is present for all measurements made in each 2-mm block of the pullback (Fig. 3). The block chemogram provides a summary of the data and does not indicate individual pixel data or the location of a measurement in the circumferential dimension.

Patient population. Patients were recruited from the population undergoing nonemergent percutaneous coronary intervention (PCI) of a de novo coronary lesion for stable coronary artery disease or ACS at 6 participating centers. The institutional review board of each center approved the study. Informed consent was obtained for all patients before the procedure.

Patients were excluded if there was evidence of ongoing ischemia in the preceding 24 h, if more than 2 separate coronary lesions were to be stented, if the target lesion had high-risk characteristics (angulated, length >20 mm, ostial location, bifurcation, reference vessel diameter <2.5 mm, angiographic thrombus), or if there was evidence of renal or liver failure, anemia, or any major systemic illness.

Study procedure and image acquisition. The target lesion for imaging, which in most cases was the culprit lesion leading to the need for PCI, was identified from the coronary angiogram as per standard clinical practice in conjunction with other localizing data obtained by noninvasive testing when applicable. Procedures were performed via the femoral or radial approach at the discretion of the operator with 6-F or larger standard coronary guiding catheters. After routine anticoagulation, the target lesion was crossed with a 0.014-inch guidewire. Dilation of the target lesion before NIRS imaging was performed at the discretion of the operator.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes
CI = confidence interval
CK = creatine kinase
IVUS = intravascular ultrasound
LCP = lipid core-containing coronary plaques
MD = Mahalanobis distance
MI = myocardial infarction
MLD = minimum lumen diameter
NIRS = near-infrared spectroscopy
PBR = pullback and rotation
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
SFR = spectral F-ratio

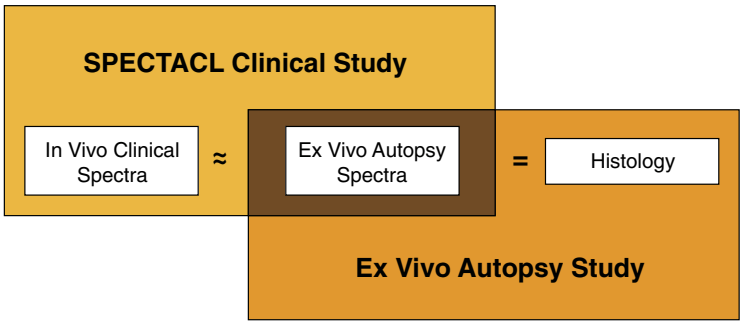

Figure 1. NIRS System Validation Strategy

Ex vivo study: the lipid core-containing coronary plaques (LCP) detection algorithm was trained from ex vivo spectra with histology as a reference gold standard and prospectively validated in an independent set of coronaries from human autopsy hearts (10). The SPECTACL (SPECTroscopic Assessment of Coronary Lipid) Clinical Study was designed to show that the spectral features of data acquired in coronaries of patients were substantially the same as the spectral features in the ex vivo study. Similarity of in vivo and ex vivo spectra would demonstrate the applicability of the LCP detection algorithm to living patients. NIRS = near-infrared spectroscopy.

A safety prerequisite for performing NIRS was successful advancement of a commercially available intravascular ultrasound (IVUS) catheter without evidence of ischemia (chest pain or electrocardiographic changes). After IVUS, scanning NIRS was performed in the target vessel. When possible, the NIRS imaging window was positioned beyond the target lesion. Scanning NIRS with automated rotational pullback was then performed at a speed of 0.5 mm/s and 240 RPM with the goal of terminating the pullback after the imaging element entered the guiding catheter. The NIRS catheter was removed, and the rest of the PCI procedure continued as planned. Angiographic data were stored

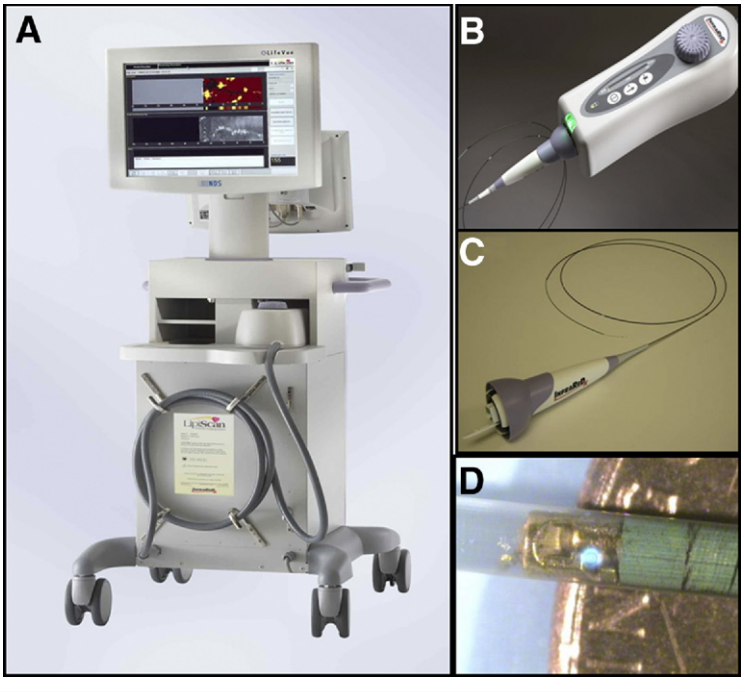

Figure 2. InfraReDx NIRS System

(A) The portable near-infrared spectroscopy (NIRS) console contains the laser light source, a computer for algorithmic data processing, and a user interface that displays the chemogram of the scanned artery. **(B)** The pullback and rotation device rotates and pulls back the imaging core. **(C)** The disposable imaging catheter contains the rotating core with optical fibers that deliver and collect near-infrared light as well as a sealed outer sheath with a guidewire provision. **(D)** Optical tip of the NIRS catheter lying on a U.S. penny.

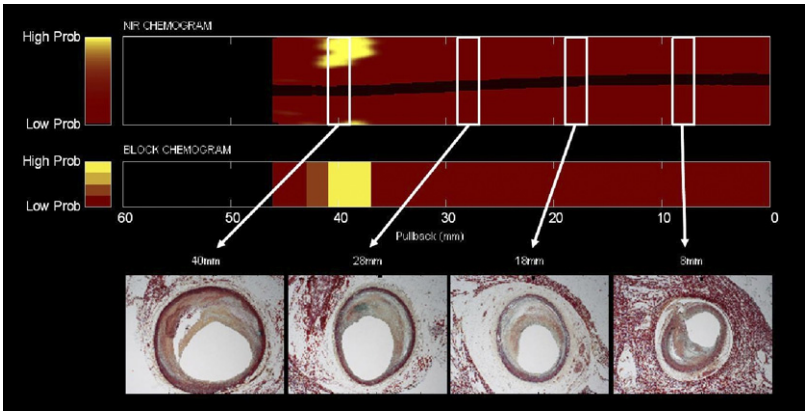

Figure 3. A NIRS Scan From a Coronary Artery From the Autopsy Study Compared With Histology

(Top) False color map of the artery wall indicating the probability of a lipid core-containing coronary plaques (LCP) of interest at each location along the length (x-axis, in mm) and circumference (y-axis, in degrees) of the scanned artery (**red** = low probability; **yellow** = high probability). This display is termed a "chemogram." **(Middle)** Summary of the presence of LCP at 2-mm intervals in 4 probability categories, termed a "block chemogram," **(Bottom)** Russell-Movat's pentachrome-stained cross-sections (5-μm thick) at 8, 18, 28, and 40 mm, respectively, along the scanned artery **(white rectangles)**. Image interpretation: in the chemogram, a prominent LCP signal is detected from 38 to 42 mm, occupying approximately 180° of circumference. The block chemogram shows that the strongest LCP signals extend from 38 to 41 mm. The near-infrared spectroscopy (NIRS) signals at 28, 18, and 8 mm indicate absence of LCP, despite the presence of diffuse plaque, which is confirmed by histology.

digitally for subsequent analysis. The NIRS data analysis was performed offline on the prospectively collected data.

Post-procedure myocardial infarction (MI) was defined as creatine kinase (CK) elevation >2 times normal with elevated CK-MB fraction and ischemic symptoms or re-elevation of CK within 24 h of the procedure of at least 50% above the previous level in ACS patients. An independent Data and Safety Monitoring Board (Appendix) reviewed all pertinent data at appropriate intervals.

Study end points. The primary end point of the study was the similarity of NIRS spectra obtained in patients to spectra previously obtained and validated by histology in autopsy specimens. Secondary end points were to obtain data supporting the expected safety of the device and to quantify the presence of LCP at target and nontarget sites.

Validation of the LCP detection algorithm in human coronary artery autopsy specimens. The LCP detection algorithm was developed and prospectively validated in a human coronary artery autopsy study (10). As reported, LCP of interest was defined as fibroatheroma >60° in circumferential extent and >200 μm in thickness on a cross-sectional histologic specimen, with a fibrous cap having a mean thickness of <450 μm. The NIRS identified localized LCP with an area under the receiver-operating characteristic curve of 0.80 (95% confidence interval [CI]: 0.76 to 0.85) in vessels 3.0 mm in diameter or less (10).

Assessment of frequency and distribution of LCP in patients in the SPECTACL study. Each chemogram from the SPECTACL dataset was evaluated for the presence of LCP. An LCP was considered to be present if at least 1 2-mm segment in the block chemogram had a strong positive reading (95% specificity that LCP is present) as signaled by a bright yellow color.

The prevalence of LCP at the target lesion was also calculated in patients in whom the target lesion could be located in the chemogram. Registration of chemographic and angiographic data was obtained by the following 4-step process. First, the target lesion was located by quantitative coronary angiography (QCA) according to the minimum lumen diameter (MLD). Second, the distance from the MLD to the distal edge of the guide catheter was calculated with the angiogram with the NIRS catheter positioned across the target lesion. Third, the location of the distal edge of the guide catheter in the chemogram was identified. Fourth, with the distal edge of the guide catheter serving as the fiducial point, the location of the MLD in the chemogram was determined according to the distance calculated in step 2. The length of the target lesion was determined by QCA.

In the few cases in which the 4-step process could not be followed, alternative approaches were taken.

In the case of missing guide catheter location (NIRS pullback did not contain data from the guide catheter or the stable positioning of the guide catheter could not be verified by angiography), the location of the start of the NIRS measurement was used as the fiducial point. With this registration method, the distance from the MLD to the starting position of the imaging core of the NIRS catheter in a cine-angiographic frame was calculated, and this distance was then projected onto the chemogram. In the case of missing guide catheter location and starting NIRS position, a combination of markers in the chemogram entered by the physician during the pullback (side-branches by angiography) and fiducial points by IVUS (side-branches) were used to determine the location of the MLD in the chemogram. In all cases, angiographic or IVUS measurements were performed blinded to the chemogram results by a core lab (Montreal Heart Institute).

Statistical analysis. ASSURANCE OF THE QUALITY OF SPECTRAL DATA. The first step in analysis of the similarity end point was to exclude data of inadequate quality, which can result from both instrument and biological causes. Instrument causes include a poor connection between the catheter and the PBR device, microscopic debris on the optical fiber faces, damaged optical fibers, system malfunction, or obstructions such as the guide wire, guide catheter, stent, or bubbles in the saline solution of primed catheters. Biological causes include excessive blood depth encountered in large arteries and features that can cause disturbances in the flow of blood such as sudden changes in lumen diameter or orientation, side-branches, or thrombi.

Inadequate spectra excluded before assessment of spectral similarity were: 1) spectra collected at locations in which the guide wire obstructed the arterial wall; 2) spectra collected when the optical tip was inside the guide catheter; 3) spectra flagged by an oscillation metric; and 4) spectra flagged by a metric indicating poor visibility of the wall due to excessive blood depth.

The oscillation metric measures the amount of oscillation in a spectrum as a function of wavelength, determined by the sum of squared differences between a smoothed and unsmoothed version of the spectrum across wavelengths. The threshold was determined from analysis of phantom, ex vivo, and in vivo spectra with known interferences (bubbles, flow disturbances, and the like). This metric identified spectra that had excessive noise due to instrument or biological causes such as those listed in the preceding text. The wall visibility metric estimates the depth of blood between the catheter and arterial wall present in each spectrum and is based on a linear regression model correlating NIRS spectral absorbance with distance to the arterial wall. The model was constructed from data collected in autopsy specimens with lumen contours from histology as a reference. The wall was considered no longer sufficiently visible when the distance to the wall exceeded 3 mm through blood. This metric determined whether the arterial wall signal was detectable or whether there was too much intervening blood between the wall and catheter attenuating the probing light. Inadequate spectra by these metrics were excluded before assessment of spectral similarity.

SPECTACL STUDY PRIMARY END POINT—ANALYSIS OF SIMILARITY BETWEEN CLINICAL AND AUTOPSY SPECTRA. Spectra identified as adequate were then assessed for similarity with autopsy spectra from the LCP algorithm calibration set with the use of 2 multivariate metrics: the Mahalanobis distance (MD), and the spectral F-ratio (SFR). The MD is a measure of the covariance-weighted distance between a point and the center of a set of points. For a validation spectrum x (in vivo) and the mean y of a set of calibration spectra (ex vivo), the MD metric is given by (in squared units):

$$MD = (x - y)' \, S^{-1} (x - y)$$

where S^{-1} is the inverse of the covariance matrix of the calibration set. Spectra are first projected from high- to low-dimensional space by partial least-squares regression, such that x and y represent scores in the projection space.

The SFR is the sum of squared residuals of the validation spectrum relative to the average sum of squared residuals of the calibration set. The spectral residual is the difference between the estimated spectrum constructed in a lower dimensional projection space spanned by the model and the actual measured spectrum. For spectral residuals e_{val} and e_{cal} corresponding to the validation and calibration spectra, respectively, the SFR is given by:

$$SFR = m\left(\sum_{k=1}^{n} e_{val\,k}^2\right) \Big/ \left(\sum_{i=1}^{m}\sum_{k=1}^{n} e_{cal\,i,k}^2\right)$$

for m calibration spectra and n wavelengths in a spectrum.

The technical adequacy of the data was assessed for each pullback of varying length. This

was accomplished by subdividing a pullback into contiguous 2-mm blocks and evaluating each for spectral adequacy. A block was judged to be spectrally adequate if >75% of the spectra within the block were spectrally adequate. A pullback, in turn, was determined to be spectrally adequate if >75% of the blocks within the pullback were spectrally adequate. This approach to evaluating data quality was similar to that used in the autopsy validation study (10).

A pullback was judged similar (i.e., a success) if at least 80% of the spectrally adequate spectra in the pullback were below the thresholds for both the MD and SFR metrics established during the autopsy calibration study and fixed before validation.

The objective of the study was to demonstrate that more than two-thirds of the adequate pullbacks from patients were spectrally similar to the spectral features observed in the autopsy calibration set. The null and alternative hypotheses, respectively, were:

$$H_0: p \leq 0.67$$
$$H_a: p > 0.67$$

where p is the proportion of pullbacks (1 pullback/patient) deemed a success by the spectral similarity measure. The study was considered to be a success if the null hypothesis was rejected with the lower 95% CI >0.67 (2-sided test for a binomial distribution, p = 0.05).

The frequency of LCP was compared between groups with a chi-square test. A p value ≤0.05 was required for statistical significance.

Statistical analysis was performed by 2 of the authors (S.T.S., M.J.H.). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

A total of 106 patients were enrolled in the study, which was conducted between January 2006 and October 2007. The demographic and baseline clinical and angiographic characteristics of the study group are summarized in Table 1. There were no major adverse events related to NIRS imaging.

The NIRS spectra were obtained in 89 (84%) of 106 patients. No data were acquired in 17 patients (16 with the primed catheter, 1 with the sealed catheter) due to instrument-related issues or the inability to cross the lesion with either the IVUS or the NIRS catheters. The reasons for missing or technically inadequate NIRS data are presented in Table 2. Figure 4 provides a summary of the distribution of patients at each step in the analysis.

Table 1. Demographic, Clinical, and Angiographic Characteristics of the Study Patients

Characteristic	
Age, mean ± SD, yrs	61.1 ± 10.0
Gender, male, n (%)	86 (81)
Clinical history, n (%)	
Hyperlipidemia	80 (75)
Hypertension	81 (76)
Diabetes mellitus	26 (25)
Prior MI	18 (17)
Prior PCI	33 (31)
Coronary artery bypass graft	3 (3)
Cerebral vascular accident/transient ischemic attack	0 (0)
Peripheral vascular disease	4 (4)
Family history of coronary artery disease	48 (45)
Congestive heart failure	6 (6)
Clinical presentation, n (%)	
Post MI	15 (14)
Unstable angina	10 (9)
Stable angina	39 (37)
Positive functional study	26 (25)
Atypical chest pain	9 (8)
Congestive heart failure	1 (1)
Other (nonacute coronary syndrome)	6 (6)
Target vessel, n (%)	
RCA	44 (42)
LAD	40 (38)
LCX	22 (21)
Mean target lesion diameter stenosis (% ± SD)	62.5 ± 9.3

N = 106.
LAD = left anterior descending artery; LCX = left circumflex artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

In those in whom data were collected, the mean pullback length was 54.4 ± 22.8 mm (range 13.6 to 116.2 mm). One patient experienced chest pain during both IVUS and NIRS imaging, which was attributed to temporary occlusion of the vessel by positioning of the devices across a narrow stenosis. The chest pain promptly resolved each time after removal of the catheter. Six of 97 (6%) patients in whom the device was actually inserted into the coronary artery experienced a periprocedural MI (mean CK-MB elevation 33.1 ng/ml). In 5 of these cases, the MI was attributed to occlusion of a side branch associated with stenting of the target vessel; in the remaining case, the MI was attributed to occlusion of a side branch associated with stenting in a nontarget vessel in which the NIRS catheter was not introduced. Distal embolization, no-reflow,

Table 2. Reasons for Missing or Technically Inadequate NIRS Data in the SPECTACL Study Population

	No. of Patients (n = 36)
Missing data	
Inability to track vessel with IVUS or NIRS catheter	7
Lack of signal from NIRS catheter	4
Console setup error	2
Jammed PBR	1
Improperly assembled accessory	1
Improper catheter handling	1
Incomplete catheter connection	1
Technically inadequate data	
Instrumental causes	
Obstructions: guide wire, guide catheter, stent, bubbles in saline of primed catheters	5
Poor connection between catheter and PBR	4
Microscopic debris on optical fiber faces	2
Damaged optical fibers	1
System malfunction	1
Biological causes	
Features causing disturbances in blood flow: sudden changes in lumen diameter or orientation, side-branches, thrombi	5
Excessive blood depth in large arteries	1

IVUS = intravascular ultrasound; NIRS = near-infrared spectroscopy; PBR = pullback and rotation; SPECTACL = SPECTroscopic Assessment of Coronary Lipid trial.

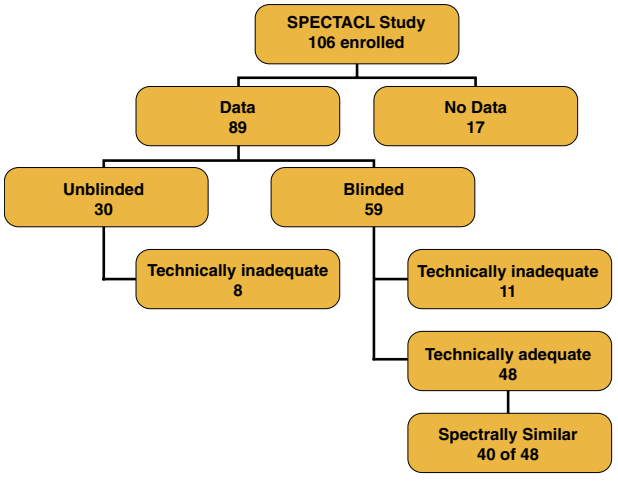

Figure 4. Final Patient Breakdown in the SPECTACL Study

No data were acquired in 17 of 106 patients enrolled, mostly due to instrument-related issues or the inability to cross the lesion with either the intravascular ultrasound or the near-infrared spectroscopy catheters. Collected data were technically inadequate in 19 of the remaining 89 patients, due to the reasons enumerated in Table 2. The primary end point was analyzed in the 48 blinded pullbacks that had technically adequate data. The frequency of lipid core-containing coronary plaques was examined in the 40 spectrally similar pullbacks from the blinded group and the 20 spectrally similar pullbacks from the unblinded group (not shown in the graph). SPECTACL = SPECTroscopic Assessment of Coronary Lipid trial.

and thrombus formation were not seen in the imaged target vessels.

Primary end point. Of the 89 patients in whom NIRS spectra were obtained, data from 30 patients (selected from the first patients studied in each center) were unblinded to determine whether the transition from ex vivo to in vivo measurement required modification of the algorithm (11). Review of the 30 unblinded chemograms indicated that in vivo spectra would not be needed to augment the calibration (autopsy) set and that the outlier thresholds selected on the basis of the autopsy data were adequate for assessment of the in vivo data. The blinded, prospective test of the primary end point was performed in the remaining cohort of 59 patients (Fig. 4).

Among the 59 patients in the blinded set, 48 (81%) had pullbacks of adequate spectral quality as prospectively specified in the Methods section. Criteria for spectral similarity were satisfied in 40 of the 48 spectrally adequate pullbacks, resulting in an 83% success rate (95% CI: 70% to 93%), thus satisfying the primary end point of the study. The median spectral similarity for each pullback was 96% with an interquartile range of 10%. Figures 5A and 5B provide graphic representations of the similarity of clinical and autopsy measurements.

Prevalence of LCP signal. An exploratory analysis of the prevalence of LCP signal was performed in the 60 pullbacks that met criteria for spectral adequacy and spectral similarity (40 in the blinded group, 20 in the unblinded group). The overall prevalence of LCP in scanned segments was 58% (35 of 60 patients).

The prevalence of LCP at target lesion sites was calculated in 57 patients in whom the target lesion was imaged. The prevalence of LCP at identifiable target lesions was 42% (24 of 57 patients) (Fig. 6). Pre-dilation of the target lesion was performed in 42% (24 of 57 patients). Lipid core-containing coronary plaque was detected in 50% (12) of pre-dilated lesions and in 36% (12 of 33) of non–pre-dilated lesions. Nontarget LCP was observed in 33% of scanned segments (19 of 57 patients) (Fig. 7). On the basis of the CASS (Coronary Artery Surgery Study) classification, the location of the target lesion sites was proximal, mid, or distal in 25% (n = 14), 63% (n = 36), and 12% (n = 7) of patients, respectively. Among the 24 target lesion sites with LCP, 17% (n = 4) were proximal, 67% (n = 16) were mid, and 17% (n = 4) were distal. Patients were subdivided into ACS and non-ACS groups on the basis of troponin and CK levels.

Specifically, patients with elevated CK (CK >180 U/l) or troponin levels (T >0.1 or I >0.4 ng/ml) were designated as ACS. Among the 57 patients in whom the target lesion was imaged, the prevalence of LCP was 53% (9 of 17) for ACS and 38% (15 of 40) for non-ACS patients (p = 0.28).

DISCUSSION

This first-in-human study demonstrates that this catheter-based system can safely perform NIRS in coronary arteries of living patients. The system obtained high-quality spectra through blood and during cardiac motion with short scanning acquisition times. Analysis of the blinded dataset demonstrates that the spectra obtained from patients are similar to previously validated autopsy spectra, thereby supporting the applicability of the chemometric algorithm for detection of LCP to patients. The algorithm identified LCP in a significant number of imaged segments in patients undergoing PCI for stable angina and ACS.

Safety of the system. No significant intraprocedural complications were noted, as expected from the characteristics of the catheter, which is similar in design and use to existing IVUS catheters. The observed 6% rate of post-procedure MI was within the reported rates (5% to 30%) for patients undergoing PCI (12–14) and was not likely related to the use of the device. Thus, no safety concerns were raised in this relatively low-risk population.

Performance of the catheter-system. Instrument-related issues prevented data acquisition in some patients. Most of these difficulties resulted from lack of signal from the catheter or operational errors. These issues were most frequently observed with the first-generation system and catheter and virtually eliminated with the adoption of the second-generation system, which simplifies the connection between catheter and PBR and uses a sealed catheter, which removes the need for priming.

Inadequate NIRS data that led to exclusion of pullbacks or failed spectral similarity metric resulted from either malfunction of the research device or the presence of signals not interpretable by the algorithm. Examples of the first category include improper optical connections or impeded rotation of the optical core, as would result from overtightening of a hemostatic valve around the catheter. Reasons for the algorithm not being able to interpret a signal include: 1) the potential effect of disturbed blood flow, such as would be seen in the presence of a side branch in a tight stenosis at a point of significant curvature, which can cause excessive oscillations in the NIRS spectra; 2) poor wall visibility due to excessive blood depth between

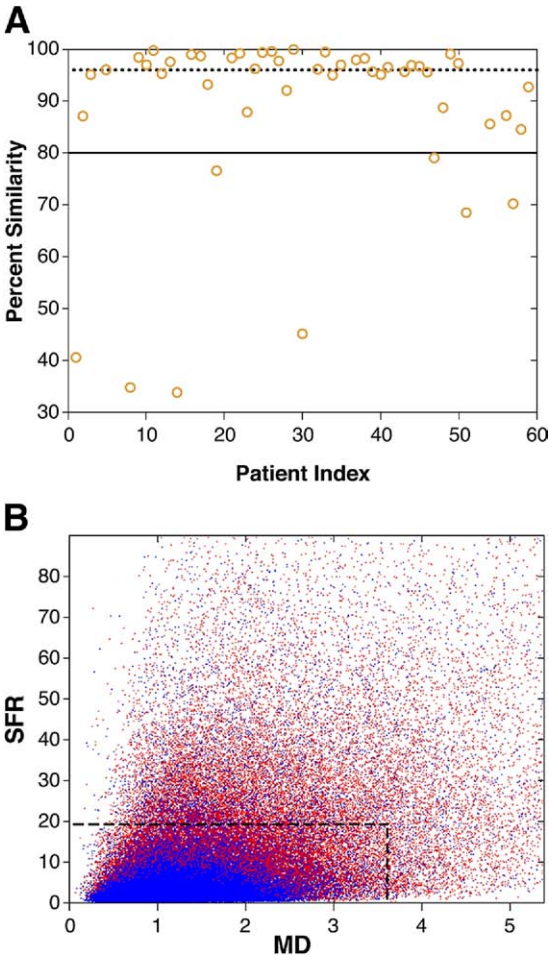

Figure 5. Spectral Similarity of Clinical and Autopsy Measurements

(A) Percent similarity of spectrally adequate pullbacks. **Dashed line** is median percent similarity (96%). **Solid line** is 80% minimum threshold for defining a spectrally similar pullback. Forty of the 48 pullbacks (83%) had a percent similarity above the threshold. Percent similarity is defined as the percentage of spectra in a pullback that are within both the Mahalanobis distance (MD) and spectral F-ratio (SFR) metric thresholds. Similarity was calculated between spectra measured in patients and calibration spectra collected in autopsy hearts. **(B)** Scatterplot of MD and SFR metrics for individual spectra in the autopsy calibration **(blue)** and patient data **(red)**. The plot shows the scatter of the 2 metrics, MD and SFR, used to assess the similarity of spectra collected in patients to those collected in autopsy specimens. **Box** shows similarity thresholds established during the autopsy calibration study for the 2 metrics. Axes were scaled to exclude the top 1% of the most extreme outliers for data point visibility. Both metrics of a given spectrum were required to be below their respective thresholds (i.e., inside the box) for the spectrum to be labeled as similar. Percent similarity for a given pullback was defined as the percentage of adequate spectra in the pullback whose MD and SFR metrics were both within the thresholds. Of the approximately 177,000 patient spectra, 89% fell within the thresholds.

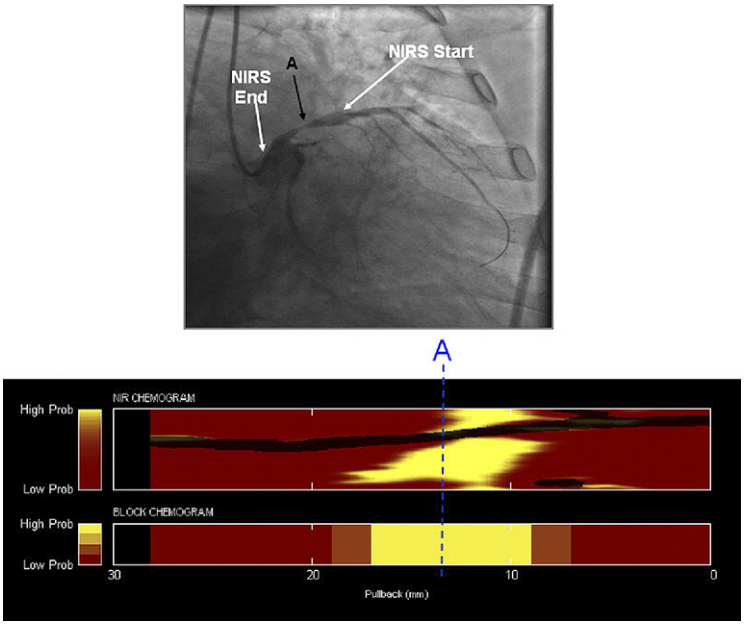

Figure 6. NIRS Scan of a Patient and Corresponding Angiogram

(Top) cineangiographic frame of the left coronary artery of a 71-year-old man with post-infarct angina. There is a severe culprit stenosis **(A)** in the proximal left anterior descending artery. **(Bottom)** the corresponding chemogram reveals a prominent, circumferential lipid core-containing coronary plaques (LCP) signal between 8 and 18 mm in the area of the culprit lesion. The narrowest area of luminal stenosis is approximately 14 mm and demarcated in the chemogram **(A)**. The block chemogram shows that the strongest LCP signals extend from 9 to 17 mm. NIRS = near-infrared spectroscopy.

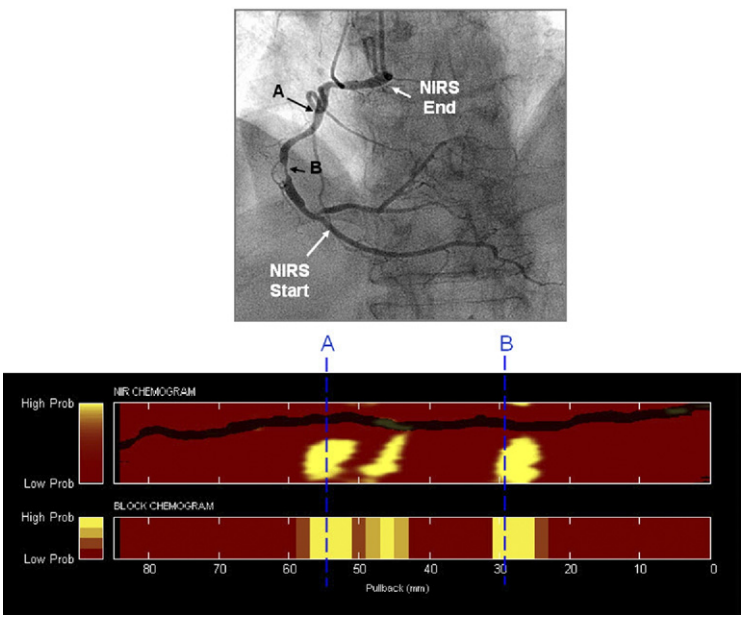

Figure 7. NIRS Scan of a Patient and Corresponding Angiogram

(Top) cineangiographic frame of the right coronary artery of a 68-year-old man with unstable angina. There is a severe, irregular culprit stenosis in the mid portion of the artery **(B)**. **(Bottom)** the corresponding chemogram reveals a prominent lipid core-containing coronary plaques (LCP) signal between 25 and 31 mm that co-localizes with the culprit stenosis. There are 2 more proximal LCP signals between 43 and 58 mm **(A)**, which probably correspond to a single plaque mass in an "angiographically normal" segment of the vessel. The block chemogram shows the strongest LCP signals between 26 to 31 mm, 45 to 47 mm, and 51 to 57 mm. NIRS = near-infrared spectroscopy.

the catheter and 1 side of the vessel wall, in which the algorithm would classify such signals as uninterpretable (inadequate data); and 3) the presence of other unknown biologic or nonbiologic signals, such as spectra from a large intraluminal thrombus. In such cases the spectra might not be recognized by the algorithm, which was trained on a calibration set without such features.

It is likely that these technical limitations will be overcome as more experience is gained with the device in a variety of clinical situations and coronary substrates. These issues notwithstanding, the primary end point of demonstrating spectral similarity between ex vivo and in vivo data was achieved.

Prevalence of LCP in patients. The relatively high prevalence of LCP signals in the chemograms in the scanned segments (58%) is likely reflective of the high pretest probability of lipid core plaque in these patients (all of whom required PCI) and selective inquiry at target sites.

There are factors that could have affected the observed prevalence of LCP at the target lesion site. In some cases, the lipid core content of the target lesion might be underestimated before measurement due to some of the lipid being "washed away" after plaque rupture. It is also possible that some target lesions that ruptured or were dilated retain lipid that is below the current threshold required for display of an LCP signal on the chemogram. The LCP(+) signal, indicated by yellow in the chemogram, is displayed when the algorithm indicates there is a high probability (>0.6 on a scale of 0 to 1.0 for each pixel) of the presence of an LCP of interest. Therefore, if a lipid signal is present but less intense (probabilities <0.6 for LCP but >0), the chemogram is designed to display a red color. A dedicated study of lesion composition could use these subthreshold lipid signals.

Situations can also be encountered in which chemogram signals might differ from histologic findings. In the autopsy validation study, Gardner et al. (10) reported that false positive readings could be caused by fibroatheromas too small or with caps too thick to meet criteria for LCP of interest or by lesions such as intimal xanthoma and pathological intimal thickening that contain significant lipid but do not have necrotic cores. False negative readings, by contrast, could be produced by necrotic cores with extensive calcification or from signals obtained in a large arterial lumen in which blood obscures the lipid signal. Both false positives and false negatives can be created by the need to impose a binary definition (lipid core plaque of a certain size present or absent) on a continuous variable.

Near-infrared spectroscopy could be used in a future study to compare the composition of culprit lesions among patient subgroups of interest. Such a study would require precise definition of the subgroups (ACS vs. non-ACS), acquisition of NIRS signals before dilation of the lesion in as many patients as possible, and larger numbers of patients.

Study limitations. The first-generation NIRS clinical system caused an unacceptably high rate of failure to obtain adequate data. Much of this problem was solved by introduction of the sealed catheter with the improved connector. However, in some instances the new system also generated uninterpretable or technically inadequate data. The sources of some of these unknown signals are discussed in the preceding text and require further investigation. The lack of repeatability data is a limitation of our study, because repeat pullbacks were not allowed as per protocol. Further studies in patients will be required to address this issue.

The correlation with a given histologic feature is not perfect, as is typical for an imaging device. Even though this device is effective for detection of LCP of interest as defined, further study will be required to assess its capability for detection of other histologic findings, such as smaller lipid plaques, thrombus, intraplaque hemorrhage, or inflammation. It is possible that use of molecular targeting agents or combination imaging technologies will enhance the diagnostic accuracy of the system. Lastly, the clinical utility of identification of the presence of LCP requires further study. A prospective follow-up study is planned in which the relationship between the identification of a lipid-core plaque and subsequent coronary events will be determined.

Summary. High-quality NIRS signals, similar to those validated in human coronary autopsy specimens, were obtained from the coronary arteries of living patients through blood and during cardiac motion with a catheter-based system. This first-in-human study supports the use of intracoronary NIRS for detection of lipid core plaques in patients undergoing PCI. This novel diagnostic capability has the potential to improve multiple aspects of the diagnosis and treatment of patients with coronary artery disease.

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Key Words: coronary disease ■ imaging ■ spectroscopy.

▶APPENDIX

The members of the Data and Safety Monitoring Board (DSMB) were John A. Bittl, MD (Munroe Hospital, Ocala, FL) (Chair), Jeffrey A. Brinker, MD (Johns Hopkins Hospital, Baltimore, MD), and James M. Ware, PhD (Harvard School of Public Health, Boston, MA). The purpose of the DSMB was to provide general oversight of the study, including reviewing the overall protocol, monitoring patient safety, and assessing the integrity of the data and results.